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DEPARTMENT OF DRUG DESIGN AND PHARMACOLOGY

Pharmacokinetic Metamodel of Morphine and Morphine-6-Glucuronide in Neonates and Adults

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BACKGROUND

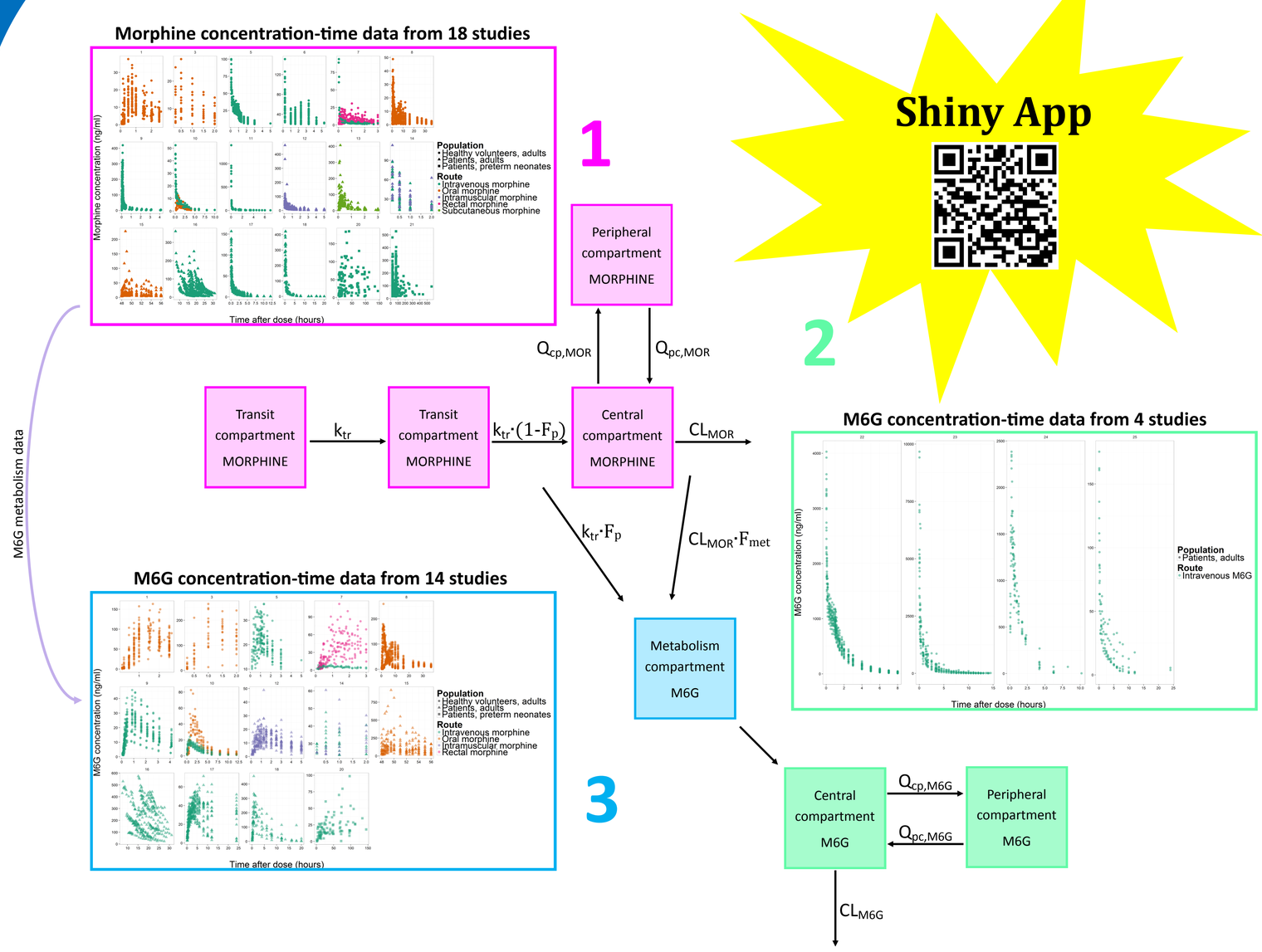
Morphine is the gold standard opioid to treat moderate to severe pain. Morphine-6-glucuronide (**M6G**) is an active metabolite and contributes to the effect of morphine [1]. The pharmacokinetics (PK) of morphine and M6G are associated with large inter-individual variability, which makes optimal dose selection challenging, especially in populations such as neonates and patients with renal impairment [2].

[1] Binning, A.R., Przesmycki, K., Sowinski, P., Morrison, L.M., Smith, T.W., Marcus, P., Lees, J.P., Dahan, A., 2011. A randomised controlled trial on the efficacy and side-effect profile (nausea/vomiting/sedation) of morphine-6-glucuronide versus morphine for post-operative pain relief after major abdominal surgery. Eur. J. Pain 15, 402-408.
[2] Somogyi, A.A., Barratt, D.T., Coller, J.K., 2007. Pharmacogenetics of opioids. Clin. Pharmacol. Ther. 81, 429-444.

AIMS

The aims of this study were to develop a **combined morphine and M6G PK metamodel in neonates and adults**, identify covariates that explain some of the large variability, and describe the **formation of M6G** after administration of morphine through different routes.

PHARMACOKINETIC MODEL



METHODS

- Morphine and M6G data from 22 studies, 686 subjects
- Various administration routes
- Healthy volunteers, preterm neonates, and patients with e.g. renal impairment
- NONMEM 7.3.0, PsN, and Pirana
- Sequential modelling of morphine and M6G data

RESULTS

- Two compartment morphine and M6G models
- Two transit compartment absorption for morphine (oral, rectal, and subcutaneous route)
- Systemic and first-pass metabolism of morphine to M6G described
- Several covariates identified including age on morphine clearance, and creatinine clearance on M6G clearance

CONCLUSION

- Some of the large inter-individual variability in morphine and M6G PK was explained with covariates
- Individual morphine and M6G concentrations can be predicted in the shiny application

Parameter	Covariate	Relationship	Equation
Morphine clearance	Postmenstrual age	Sigmoidal	$\frac{PMA^{\gamma}}{PMA^{\gamma}+TM_{50}^{\gamma}} \rightarrow \frac{PMA^{2.31}}{PMA^{2.31}+113^{2.31}weeks}$
	Age (adults)	Power	$\left(\frac{age}{median\ age}\right)^{AGECOV} \rightarrow \left(\frac{age}{37.5\ years}\right)^{-0.336}$
M6G clearance	Creatinine clearance	Power	$\left(\frac{CR_{CL}}{112.5\frac{ml}{min}}\right)^{CRCLCOV} \rightarrow \left(\frac{CR_{CL}}{112.5\frac{ml}{min}}\right)^{0.917}$
Morphine and M6G central volume	Venous sampling site	Linear	$(1+VENCOV) \rightarrow (1+0.0936)$
All clearances and volume	Body weight	Power, fixed exponent (0.75 for clearances, 1 for volumes)	$\left(\frac{weight}{70\ kg}\right)^{0.75}$ or $\left(\frac{weight}{70\ kg}\right)^{1}$

Mean transit time	
0.729 h	Oral solution, oral immediate-release tablet, and rectal solution
14.6 h	Oral modified-release tablet
0.310 h	Subcutaneous injection
Bioavailability	
14.4%	Oral solution and oral immediate-release tablet
18.8%	Oral modified-release tablet and rectal solution
Systemic metabolism	
12.8%	All
First-pass metabolism	
20.8%	Oral solution, oral immediate-release tablet, oral modified-release tablet, and rectal solution

Link to shiny app: https://unicph.shinyapps.io/MorphineMetamodel/

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